REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the remarks which follow.

By this amendment Applicants have cancelled claims 4, 8 and 9, and have amended claims 1, 5, 7, 15-16, 18-20. These amendments are supported in the as-filed specification.

Claim Objections

In claim 1, the typographical mistake "step" has been corrected with "steps".

In claim 7, the species have been properly capitalized: "*Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus casei*"

The Examiner has raised objections to claims 1-7 and 16 because of certain informalities. These objections are respectfully traversed.

In claim 16, the term "concentrated at warm under vacuum" has been reworded as "concentrated warming under vacuum".

Claim Rejections – 35 USC § 112

Claims 1-3, 5-18 and 20 have been rejected under 35 U.S.C. § 112, second paragraph, for omitting essential steps, namely, providing/contacting and concluding/correlating steps. This rejection is respectfully traversed since Applicants believe that the claims as-filed included all of the required essential steps. In claim 1:

- *providing/contacting step* is step (i) wherein the recited active step is the inoculating of the starting milk or milk serum suspension with non-modified (wild-type) micro-organisms;

- *detecting/reacting step* is step (ii) wherein fermentation is "allowed" (using same wording as in TORINO experimental section) to proceed for a certain period of time under controlled pH; and,

- *concluding/correlating step* is step (iii) wherein the desired product galactose is recovered.

While Applicants believe that the pending claims as filed included all of the required essential steps, in the interest of greater clarity, claim 1 has been amended. The amendments to claim 1 also take into consideration the second 35 USC §112, second paragraph, rejection recited immediately below.

Claims 1-3, 5-18 and 20 have also been rejected under 35 USC § 112, second paragraph, for "failing to particularly point out the subject matter which Applicants regard as the invention".

The claim rejection is for insufficient antecedent basis because of the recited limitations "the solution ... from step (i)" and "the desired galactose solution ... from step (ii)". To overcome this rejection, the word "suspension" (which is a synonym for solution and more appropriate for use with milk or milk serum) has been introduced in claim 1-step (i).

Claims 16 and 17 have been rejected for insufficient antecedent basis because of the recited limitation "the biomass". To overcome this rejection the word "biomass" has been introduced in claim 1-step (iii).

Claims 1-3, 5-18 and 20 have been rejected for being indefinite, because claims 1 and 18 are unclear. To overcome this rejection, claim 1 has been amended by changing the phrase "not subjected to any preliminary and purification treatment" to "not subjected to any preliminary removal of the protein portion of milk". This Amendment finds support in the specification at page 1, [0004].

Claims 1-3 and 5-20 have been rejected because the term "non-modified micro-organisms" is unclear. To overcome this rejection, claim 1 has been amended by changing the term "non-modified" into "wild-type".

Claim 20 has been rejected for insufficient antecedent basis in the limitation "said base, strong or weak, of inorganic origin is selected in the group consisting of ... sodium hydroxide, ... ammonia " To overcome this rejection, claims 15 and 20 has been amended, as suggested by the Examiner, as follows:

"... said base of inorganic origin added in step ii) is
a strong base selected from the group consisting of sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide and calcium carbonate, or
a weak base selected from the group consisting of ammonia."

Claim 8 has also been rejected as being incomplete for omitting essential steps because the term "allowed" is unclear. Claim 8 has been cancelled rendering the rejection moot.

The limitations formerly found in now cancelled claims 8 and 9 have been included in step ii) of claim 1.

In view of the foregoing, the § 112, second paragraph, rejections have been overcome and should be withdrawn.

Claim rejections - 35 USC § 102

Claims 1-3, 5-6, 8-15 and 18-20 have been rejected under 35 USC §102(b) as being anticipated by TORINO. This rejection is respectfully traversed.

TORINO teaches how the heterofermentative pattern of a particular *Lactobacillus* helveticus ATCC 15807 ("a ropy strain producing high amounts of EPS") is influenced by pH. This teaching is influential for the dairy industry (see introduction) since it could employ this bacterium as an EPS-producing strain to be "incorporated into starter cultures in order to avoid the use of additives of plant or animal origin" and to allow "the elaboration of low-fat mozzarella and mozzarella-like cheeses since the EPS synthesised enhances the estensibility of these products".

TORINO also teaches how to isolate, quantify, and characterize the EPS (exopolysaccharides) obtained from the fermentation step. TORINO also discloses how the residue of fermentation (lactose) and hydrolysis products (glucose and galactose)

have been analytically determined using standard HPLC techniques. However, TORINO ***does not teach*** how the galactose obtained from the fermentation can be recovered and, therefore, is silent with respect to the step iii) of the present invention related to the removal of the biomass. Certainly, HPLC is not a suitable recovery technique, especially if the recovery has to be done on an industrial scale. Moreover, it is noteworthy that from TORINO's point of view, galactose is a side product (or at least an indirect indicator of the EPS production) of the fermentation since its main focus is to obtain EPS and not monosaccharides or other end products. Therefore, it appears that galactose is accidentally found in this piece of prior art.

From a careful examination of the graphs (Figs. 2 and 3) reported by TORINO, it can be calculated that TORINO's experiments are carried out on milk with a starting content of lactose of about 4% w/w which yields, after 24 hours at pH 6.2, a galactose content of about 0.7% w/w (which notably decreases for time periods lower or higher than 24 hours) which represents a very low galactose yield, which would not be economically advantageous for an industrial scale isolation. Moreover, in the graph (Fig. 2) at 24 hours and pH 6.2 what seems to be almost zero lactose is actually about 10 mmol/L which represents about 50% by weight of the 40mmol/L of galactose (Fig. 3 at 24 hours at ph 6.2). From a mixture such as this, galactose could never be isolated with acceptable purity since it would, quite obviously, be contaminated by lactose.

TORINO teaches that "*L. helveticus* ATCC 15807 released glucose and galactose moieties into the medium at different rate according to the incubation time and culture pH" and "the fate of both sugars was also dependent on both parameters". It, therefore, teaches that a bacterium which is *prima facie* galactose positive (as *L. helveticus* as taught by TURNER in *Applied Environmental Microbiology* 1983, 45(6), 1932-1934 should be), could change to galactose-negative depending on the incubation time and culture pH. In any event, TORINO gives no indication that the observed pH dependent pattern determined just for *L. helveticus* ATCC 15807 strain can be generalized to the other *L. helveticus* strains or, more generally, to the other *Lactobacilli* strains. TORINO is also silent with respect to what happens to fermentation patterns, depending on

incubation time and culture pH, when mixtures of two or more micro-organisms of bacteria are used as they are in the present invention (examples 1, 3 and 4).

Moreover, TORINO is silent with respect to what is the fermentation pattern, if, after fermenting for a given period of time at a given pH, a further step is performed in which the fermentation is allowed to proceed without controlling the pH.

In light of the aforementioned considerations, the present invention distinguishes over TORINO with respect to:

- the use of a non-selected strain of a micro-organism specie (also in mixture of two or more species);
- the fermentation condition at pHs different from 4.5, 5.0 and 6.2 and, particularly at pH just <7.5 (see examples 1-5); and
- the industrial scalable method for recovery of the galactose produced by the fermentation.

In view of the foregoing, the claims distinguish over TORINO and, accordingly, the § 102(b) rejection has been overcome and should be withdrawn for failure to establish a *prima facie* case of anticipation.

Claim rejections - 35 USC § 103

Claims 1-3 and 5-20 stand rejected under 35 U.S.C. § 103(a) over the combination of the ACUNA article, MOORE, U.S. 2,974,044 and the TURNER article. This rejection is traversed.

Claims 1-3 and 5-20 also stand rejected under 35 USC § 103(a) over GALZY, U.S. 3,981,773 in view of ACUNA, MOORE and TURNER. This rejection is traversed.

While Applicants agree that pH, temperature and reaction times are known variables effecting microbial/enzymatic reactions, but as TORINO teaches for *L. helveticus* ATCC 15807 and as ACUNA teaches for *S. Thermophilus 404* and *L. Bulgaricus 398* and mixture thereof, one of ordinary skill in the art would expect from studying these references that each micro-organism has its own fermentation pattern

which is multi-dependent on these variables and is *a priori* unpredictable. Therefore, where there is no teaching on what the fermentation pattern is at a given pH, or for a given period of time, it would be "*entirely unobvious*" to employ conditions selected from the known ones for a desired purpose. The situation is even much more complex when a mixture of micro-organisms is used.

ACUNA only teaches the selected strains *S. themophilus 404*, *L. bulgaricus 398* and mixtures thereof at pH 6.5, 5.8 and 6.15, respectively, and the relationships between the substrate (lactose) and product (galactose and lactic acid) concentrations concerning lactic acid fermentations with the aim of improving various processes relevant to the dairy industry. ACUNA's teaching, therefore, is directed to how to analytically determine the concentrations of lactose, galactose and lactic acid by means of HPLC. Nothing is taught, disclosed or even suggested regarding the removal of the biomass issuing from the fermentation step. Thus, ACUNA teaches conducting an analytical determination for lactose, galactose and lactic acid by means of HPLC.

ACUNA uses a fermentation medium that is somewhat of an artifact (since it also contains yeast). It is not the simple milk or milk serum derived from the dairy industry which is employed in the claimed invention.

As the Examiner states at page 10, last paragraph, of the Office Action, ACUNA is silent with respect to the consumption of glucose and what occurs when fermenting for periods of time > 7 hours and, moreover, ACUNA is silent with respect to:

- fermenting with non-selected strains of a micro-organism specie and mixture thereof and fermenting with mixture of more then two micro-organisms;

- fermentations that proceed for a period of time while the pH is controlled, and then left to proceed without controlling the pH;

- fermenting at pHs which are different than 6.15 for mixed cultures; and

- the method of recovering galactose on an industrial scale since HPLC is not applicable for industrial recovery.

Therefore, the end products of the claimed invention are necessarily different from and distinguishable over ACUNA's.

The nature of the end product obtained by ACUNA is not clear, since from the reported graphs it is not possible to deduce the final ratio of lactose/galactose w/w which is crucial for a successful galactose crystallization, but is not at all relevant for the dairy industry (which is the purpose of the ACUNA article).

MOORE teaches a method for the production of carotenoids by means of fermentation processes. It has nothing whatsoever to do with galactose production nor to lactic acid fermentations. The notion that the pH of a suspension wherein acids are formed and could be adjusted with the addition of a base, and that bases such as NaOH, KOH, $Ca(OH)_2$, NH_4OH, Na_2CO_3 are all equivalent, is obvious to any person with a basic knowledge of chemistry, since all these bases share the Markush structure OH^-, which is produced when these bases are dissolved in aqueous solutions. What is ***entirely unobvious*** to one of ordinary skill in the art is when, how, and for what use this notion can be employed "in a process for the production of galactose", rather than the production of carotenoids or cheeses.

TURNER teaches *Lactobacilli* which are not only incapable of fermenting galactose and which are not useful to the dairy industry, but it is also silent with respect to how galactose, once produced, can be recovered on an industrial scale. Moreover, TURNER teaches the production of galactose at a pH ranging from 3.77 to 4.27 Nothing whatever is said with respect to the galactose residue obtained from fermentation at $5<pH<7.5$. Therefore, with respect to TURNER, the end products of the present invention are necessarily different and distinguishable.

The GALZY reference teaches how to produce galactose by means of fermentations using mutated or selected micro-organisms (not wild-type or unselected) and discloses that in order to do so, the micro-organisms have to be of gal-negative character. GALZY is silent with respect to fermenting under a pH controlled environment and eventually further fermenting under an uncontrolled pH environment. GALZY is also silent with respect to fermenting for 16-24 hours. Therefore, with respect

to GALZY the present invention differs with respect to the micro-organisms, the pH environment and the fermentation times, resulting in end products that are necessarily different and distinguishable.

Moreover, taking into account the teachings of the ACUNA, TURNER and GALZY references, the only thing which would have been obvious to one of ordinary skill in the art was to use only pure selected gal-negative micro-organisms or a mixture containing at least one gal-negative microorganism. However, the present invention goes beyond this technical prejudice by using the most economical micro-organisms available for lactic acid fermentation without selecting them from among gal-negative strains.

In the claimed invention the gal-negative character of the employed microorganisms, even if obviously preferred, is not crucial and, in fact, in the claimed invention Applicants have used microorganisms (and mixtures thereof) which, even if known to be gal-negative (such as *S. thermophilus*), ***have unexpectedly exhibited***, at the end of the presently claimed process, a gal-positive character. This has been verified by analyzing the enantiomeric form of the obtained lactic acid which is racemic (D- and L-lactic acid) and, therefore, the micro-organisms used (and mixtures thereof) can be classified as gal-positive (according to TURNER's teachings) and should be associated with low levels of galactose. Surprisingly and contra to the conventional thinking, the ***claimed invention allows one to obtain high levels of galactose***.

Therefore, it would not be *prima facie* obvious to employ the claimed process which comprises:

i. inoculating milk or milk serum with the most economical (non-modified and non selected) wild-type microorganisms (preferably in mixture of two or more) able to hydrolyse lactose being able to grow consuming glucose but not necessarily being gal-negative strains;

ii. fermenting for 16-24 hours (times not taught by ACUNA which ferments only for 5-7 hours) at a constant pH value, chosen in the interval $5.0<pH<7.5$, maintained by adding an inorganic base (TURNER is silent with respect to fermenting at pH out of the range 3.77 – 4.27 not maintained but just detected), eventually further fermenting without maintaining pH,

thus obtaining a suspension enriched in galactose and poor in lactose and glucose; and

iii. recovering a galactose solution as by removing the biomass coming from fermentation step.

In view of the foregoing, the claims serve to distinguish over the combination of references. Thus, the two (2) § 103(a) rejections have been overcome and should be withdrawn since the Examiner has failed to establish a *prima facie* case of obviousness.

The issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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